REMARKS

Favorable reconsideration of the present application is respectfully requested in view of the above amendments and the following remarks. Claims 42, 43, 47-57, and 113 are pending in the instant application and are currently under consideration. Claims 42, 47-49, 51, and 57 have been amended, and new claims 114-116 have been added to more particularly point out and distinctly claim certain subject matter of Applicants' invention. Please cancel claims 43, 52-56, and 113 without acquiescence to any rejection and without prejudice to prosecution of the subject matter in a related divisional, continuation, or continuation-in-part application. Support for these amendments may be found throughout the specification and claims as originally filed, which may be found, for example, at page 14, line 17 through page 15, line 2; at page 23,lines 14-15; and at page 40, line 21 through page 41, line 12. No new matter has been added.

REJECTIONS UNDER 35 U.S.C. § 102

The PTO rejects claims 42, 43, and 113 under 35 U.S.C. § 102(b) as allegedly being anticipated by Neckelmann et al. (*Proc. Natl. Acad. Sci.* 84:7580-84 (1987)). Specifically, the PTO asserts that Neckelmann et al. disclose (a) isolation of a cDNA clone encoding ANT1 from human skeletal muscle; (b) a polypeptide sequence that is 98.3% identical to SEQ ID NO:31; (c) in vitro transcription and translation of the ANT polypeptide; (d) the isolation of the polypeptide on a polyacrylamide gel; and (e) a protein containing more than 30 contiguous amino acids identical to SEQ ID NO:31.

The PTO also rejects claim 113 under 35 U.S.C. § 102(a) as allegedly being anticipated by Marzo et al. (*Science* 281:2027-2031 (1998)). The PTO asserts that Marzo et al. disclose a fragment of an isolated recombinant ANT1 polypeptide, wherein the fragment comprises at least 30 contiguous amino acid residues of the sequence set forth in SEQ ID NO:31.

Applicants respectfully traverse these rejections and submit that the documents cited by the PTO fail to disclose each and every element of the instant claim; therefore, no *prima facie* case of anticipation has been established. Applicants respectfully submit that the rejections of claims 43 and 113 over Marzo et al. and over Neckelmann et al. are rendered moot in view of

the amendments submitted herewith, which include cancellation of claims 43 and 113 without acquiescence or prejudice. Applicants' invention is directed, in pertinent part, to an isolated recombinant human adenine nucleotide translocator-1 (ANT1) polypeptide comprising the amino acid sequence set forth in SEQ ID NO:31, wherein the recombinant human ANT1 polypeptide is capable of binding to an ANT ligand and is produced by a method comprising culturing a host cell that contains a recombinant expression construct comprising at least one regulated promoter operably linked to a nucleic acid encoding the ANT1 polypeptide.

Applicants submit that Neckelmann et al. fail to teach or suggest an isolated recombinant human ANT1 polypeptide comprising the sequence set forth in SEQ ID NO:31 *that is capable of binding an ANT ligand.* The cited document also fails to teach or suggest that the recombinant human ANT1 polypeptide is produced by culturing a host cell that contains a recombinant expression construct comprising at least one regulated promoter operably linked to a nucleic acid encoding the ANT1 polypeptide. Neckelmann et al. merely describe screening and cloning from a cDNA library a nucleotide sequence that encodes a human ANT polypeptide, transcribing mRNA from the identified cDNA, and expressing the transcribed mRNA in an *in vitro* translation system, which is a cell-free system that lacks a host cell comprising a recombinant expression construct having a regulated promoter.

Contrary to the assertion made by the PTO with respect to product-by process claims (Action, at page 6, lines 4-6), the presently claimed polypeptide is readily distinguishable over the protein of Neckelmann et al. As discussed below and for reasons previously made of record, including those provided in the Declaration under 37 C.F.R. § 1.132 of Dr. Christen Anderson as submitted on November 3, 2003, the subject invention recombinant ANT polypeptide, which is produced by culturing a recombinant host cell comprising a recombinant expression construct comprising a regulated promoter, offers the unobvious difference over the prior art of an ANT1 polypeptide that is capable of binding an ANT ligand. The recited process steps thus "impart distinctive structural characteristics to the final product" (see M.P.E.P. § 2113), namely the proper conformational folding of the protein such that it is capable of binding an ANT ligand, which characteristics are absent from the prior art. This is precisely the exception stated in the M.P.E.P. Section 2113 passage, which was cited by the PTO in its

allegation that the claimed subject matter is not readily distinguishable over the protein of Neckelmann et al.

By contrast, Neckelmann et al. fail in any way to provide an ANT polypeptide that is capable of binding an ANT ligand, since the polypeptide described by Neckelmann et al. results from a cell-free translation system that lacks any cellular protein-folding mechanisms or renaturation steps, and is then solubilized in the well known denaturing detergent sodium dodecyl sulfate, where such a denaturing step prevents ligand binding. For reasons given below and previously made of record, at the time of filing the instant application the state of the art had not achieved routine refolding and reconstitution of ANT polypeptides to arrive at properly folded ANT proteins. Hence, where Neckelmann et al. are silent with respect to whether or not the polypeptide disclosed therein is capable of binding to an ANT ligand, the PTO has the burden of showing that the polypeptide of Neckelmann et al. *necessarily* has been properly folded such that it is capable of binding an ANT ligand.

As discussed below, at the time of filing the present application, the ordinarily skilled artisan would have had absolutely no basis for concluding that the polypeptide of Neckelmann et al. is *necessarily* capable of binding an ANT ligand. Moreover, by alleging that "the protein of Neckelmann et al. is considered patentably indistinguishable from the protein of Claim 42" (Action, page 6, lines 3-4), the PTO improperly asserts that the prior art inherently discloses what is in fact a missing piece of evidence–that the polypeptide is capable of binding an ANT ligand. It is well settled that the PTO cannot rely on missing extrinsic evidence from the prior art as being inherently disclosed therein, and that the burden of providing such evidence falls on the PTO, not on applicants. Accordingly, the PTO has failed to meet its burden of establishing that the ability to bind an ANT ligand is *necessarily* disclosed by Neckelmann et al., or that the subject matter of the presently claimed invention is inherently suggested in the prior art.

M.P.E.P §2112 provides that:

> In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the

> applied prior art. *Ex parte Levy*, 17 USPQ2d 1461, 1464 (BPAI 1990) (emphasis in original).

Accordingly, Applicants submit that the burden remains with the PTO to supply the requisite basis in fact and/or technical reasoning, where mere conjecture on the part of the PTO (that the polypeptide of Neckelmann et al. is "indistinguishable" from the polypeptide of claim 42 and thus would be expected to be capable of binding an ANT ligand, with no suggestion of such in the art) does not suffice as a finding that the prior art reference contains a disclosure that anticipates the presently claimed invention. Furthermore, the PTO has offered no evidence making clear that "the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." (*Continental Can Co. USA v. Monsanto Co.*,948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991)).

According to section 2112 of the M.P.E.P.:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1995, 1997 (Fed. Cir. 1993) (emphasis in original).

Further, the M.P.E.P. states that:

> To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' *In re Robertson,* 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

Applicants respectfully submit that the Examiner has not met the burden of making it clear that the missing descriptive matter is necessarily present in the cited prior art. Applicants therefore respectfully submit that the Action has not set forth a *prima facie* case of anticipation. Accordingly, Applicants submit that the claims meet the requirements for novelty under 35 U.S.C. § 102 and respectfully request that these rejections be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 103(a)

The PTO rejects claims 42 and 43 under 35 U.S.C. § 103(a) as allegedly obvious over Rojo and Wallimann (*Biochim. Biophys. Acta* 1187:360-67 (1994)), Marzo et al. (*Science* 281:2027 (1998)), Kramer (*Methods in Enzymol.* 125:610-18 (1986)) in view of Neckelmann et al. (*Proc. Natl. Acad. Sci.USA* 84:7580-84 (1987)) and Fiore et al. (*Biochimie* 80:137 (1998)). The PTO asserts that it would have been obvious to a person having ordinary skill in the art to isolate human ANT1 having the sequence disclosed in Neckelmann et al. using routine isolation procedures such as those taught in Rojo and Wallimann, Marzo et al., and/or Kramer. The PTO asserts that the ordinarily skilled artisan would have been motivated to isolate human ANT1 to characterize the protein, given the teachings of Fiore et al. that increased expression of ANT1 is observed in the muscle of patients with myoclonic epilepsy associated with ragged-red fibers and myopathy, encephalopathy, lactic acidosis, and stroke-like episodes.

Applicants traverse these grounds of rejection and respectfully submit that the PTO has not established a *prima facie* case of obviousness. *See In re Mayne*, 104 F.3d 1339, 1341-43, 41 U.S.P.Q.2d 1451 (Fed. Cir. 1997) (PTO has the burden of showing a *prima facie* case of obviousness.). The PTO must show (1) that the references teach or suggest all claim limitations; (2) that the references provide some teaching, suggestion, or motivation to combine or modify the teachings of the prior art to produce the claimed invention; and (3) that the combined teachings of the references indicate that by combining the references, a person having ordinary skill in the art will achieve the claimed invention with a reasonable expectation of success. When rejection of claims depends upon a combination of prior art references, a teaching, motivation, or suggestion to combine the references must exist. (*See In re Rouffet*, 149 F.3d 1350, 1355, 47 U.S.P.Q.2d 1453 (Fed. Cir. 1998)).

Contrary to the assertion in the Action at page 8, lines 3-8, and for reasons also given above, the presently claimed ANT1 polypeptide is patentably distinguishable over the prior art because the manufacturing process steps "impart distinctive structural characteristics to the final product" and define the product which is made (see M.P.E.P. § 2113). The claimed

recombinant ANT1 polypeptide, produced by recombinant expression in host cells using a regulated promoter, retains a conformational structure having the ability to bind an ANT ligand, and therefore possesses a distinguishing structural feature that is absent from any combination of the publications cited by the PTO. The cell-free translation system of Neckelmann et al. lacks any cellular protein-folding apparatus, and the resulting cell-free products described by Neckelmann et al. are denatured in an ionic detergent in a manner that destroys the protein conformation required for ligand binding. The other cited documents describe non-recombinant processes for obtaining ANT proteins from avian and non-human mammalian sources, which proteins possess distinct structures and are not made according to the presently recited process steps. The non-recombinant ANT proteins of the prior art also necessarily cannot be produced using a regulated promoter as recited in the instant claims, and therefore cannot provide the related advantages associated with this feature of the claimed invention (see, *e.g.*, specification at page 14, line 21 through page 15, line 2; page 15, lines 19-28; page 31, lines 4-16).

Applicants submit that the cited documents, alone or in combination, fail to teach or suggest each and every limitation of the claimed invention. In particular, as also discussed above and for reasons previously made of record, the PTO fails to establish that absent the present application, a person having ordinary skill in the art would reasonably have expected successfully to isolate the claimed recombinant ANT1 polypeptide that is capable of binding an ANT ligand. As conceded by the PTO, none of Rojo and Wallimann, Marzo et al., or Kramer et al. teach or suggest an isolated recombinant human ANT1 polypeptide having the amino acid sequence set forth in SEQ ID NO:31. The cited documents, even including Neckelmann et al. and Fiore et al., also fail to teach or suggest an isolated recombinant human ANT1 polypeptide capable of binding an ANT ligand and produced by the recited method.

The disclosures of Neckelmann et al. are discussed above, specifically insofar as this document fails to suggest that the polypeptide described therein is capable of binding an ANT ligand; by using a cell free *in vitro* translation system Neckelmann et al. further fail to suggest recombinant ANT expression using a host cell. With regard to Neckelmann et al., and also with respect to any other documents cited by the PTO, the PTO errs in its allegation that

"one of ordinary skill would have expected that human ANT1 could . . . be isolated by prior art methods" (Action, at page 9, lines 16-17). According to section 2141.02 of the M.P.E.P.:

> Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1995 (Fed. Cir. 1993).

Further on this point, and for reasons given above, in view of the evidence which Applicants have previously provided (*e.g.,* Anderson Declaration) regarding failure of the prior art to express recombinant ANT proteins and uncertainty in the art with respect to proper ANT folding and functional reconstitution, the PTO has failed to meet its burden of establishing that the recited characteristic of ANT ligand binding must necessarily flow from the teachings of the prior art. The PTO fails to provide any evidence that recombinant ANT expression was known to the prior art, and errs in citing documents describing isolation of non-recombinant ANT proteins since the PTO is unable to establish that these compositions necessarily possess the distinctive structural characteristics of the presently claimed subject matter.

Accordingly, and further to the remarks presented herein, the prior art fails to suggest, and was unable to produce, the isolated polypeptide as presently claimed. Therefore, no combination of any of the cited documents teaches, suggests, or provides motivation to arrive at the claimed invention. With respect to Fiore et al., Applicants respectfully disagree with the assertion in the Action that Fiore et al. provide the requisite motivation for an ordinarily skilled artisan to combine the cited documents to achieve Applicants' invention. Fiore et al. describe pathologies that may be associated with mitochondrial ANT dysfunction, but Fiore et al. do not even remotely suggest the desirability of combining any of the other cited documents to achieve Applicants' invention, an isolated recombinant human ANT1 polypeptide.

Applicants therefore further submit that none of the cited documents, alone or in combination, teaches or suggests that an ordinarily skilled person would achieve Applicants' invention with any reasonable expectation of success. Applicants respectfully disagree with the assertion by the PTO that the claimed invention was within the ordinary skill in the art to make and use the claimed recombinant human ANT polypeptide according to methods described in the

cited documents in combination with any other prior art at the time the present invention was made.

Applicants submit that a person having ordinary skill in the art could not, in view of the art, reasonably have expected to express successfully either a yeast ANT polypeptide or a human ANT polypeptide in bacteria at the time Applicants' invention was made. Heimpel et al. (*J. Biol. Chem.* 276:11499-506 (2001)), a document available to the public only subsequent to the filing date of the present application, conclude that "the *E. coli* system does not express yeast AAC2 and mammalian AAC, such as human AAC1, due to unfavorable codon usage." (*See* Heimpel et al., at page 11504, first column). Even substitution of the unfavorable codons in the yeast AAC2-encoding polynucleotide, however, failed to increase expression in *E. coli* of the yeast transporter. Heimpel et al. further state that "renaturation/reconstitution of the AAC from inclusion bodies posed a challenge." (*See* page 11504, second column). Heimpel et al. thus provide evidence of failure by the art to express ANT in *E. coli* well after the filing date of the instant application (*see* related U.S. Application No. 09/185,904, cited in Response filed November 25, 2003, made of record in the instant application, particularly Action therein dated February 20, 2004, at page 3).

Applicants' invention is also nonobvious in view of Hatanaka et al. (*Biol. Pharm. Bull.* 24:595-99 (2001)), another document that exemplifies the state of the art well after the filing date of the present application. Hatanaka et al. describe that human ANT (AAC1) specific RNA was *not* expressed in the yeast recombinant expression system disclosed therein, and that only when human ANT amino-terminal coding sequences were replaced with yeast amino-terminal coding sequences was the chimeric yeast-human ANT polypeptide expressed in yeast mitochondrial membranes (*see* Hatanka et al., page 596-597). By contrast, in the present application, Applicants teach in a working example that human ANT-encoding RNA, without modification to include nucleotide sequences encoding a polypeptide tag for ANT detection or isolation, and without any other modification, was expressed in a yeast recombinant expression system (*see* page 83, line 13 through page 86, line 3).

Applicants respectfully submit that Hatanaka et al. and Heimpel et al. demonstrate that ordinarily skilled artisans, years after the filing date of the present application, were

unsuccessful in making an isolated recombinant ANT polypeptide. Therefore, an ordinarily skilled artisan at the time the present invention was made would not have combined the teachings of Cozens et al. and Adrian et al. successfully to achieve Applicants' invention.

Applicants also submit, as discussed in previous submissions of record, that nonobviousness of the claimed invention is supported by secondary factors such as a long-felt need and the failure of others to achieve Applicants' invention (*see* Declaration under 37 C.F. R. § 1.132 of Dr. Christen Anderson, submitted November 3, 2003). The Declarant discussed in detail the state of the art at the time Applicants' invention was made. Briefly, for example, Fiermonte et al. (*Biochem. J.* 294:293-99 (1993)) taught that while the oxyglutarate mitochondrial membrane transport protein could be expressed in bacteria, expression of ANT was toxic to bacteria, resulting in only low level expression of a non-functional ANT polypeptide. Miroux *et al.* (*J. Mol. Biol.* 260:289-98 (1996)) also attempted to express various recombinant proteins, including mammalian ANT, in a bacterial expression system but encountered multiple difficulties, including toxicity to host bacteria cells, poor solubility of the recombinant product, and accumulation of recombinant ANT in inclusion bodies (*e.g.*, Miroux et al., at pages 290-291 and Table 1). The state of the art *after* the date on which Applicants' invention was made, as exemplified by Heimpel et al. discussed herein, also illustrates the failure of others to make a recombinant ANT polypeptide that is capable of binding to an ANT ligand.

Accordingly, Applicants respectfully submit that the present invention is nonobvious, satisfying the requirements of 35 U.S.C. § 103(a), and request that this rejection be withdrawn.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (WRITTEN DESCRIPTION)

The PTO rejects claims 47-57 under 35 U.S.C. § 112, first paragraph, asserting that the claims are directed to subject matter that is not adequately described in the specification. More specifically, the Action asserts that (1) non-human sequences are known that are greater than 95% identical to SEQ ID NO:31; (2) the specification provides only one species of the genus; (3) all human ANT sequences are not presently known; and (4) the specification has not provided sufficient written description as to what sequences are considered human.

Applicants respectfully traverse these grounds of rejection and submit that Applicants possessed the claimed invention, as disclosed in the present specification and recited in the instant claims, at the time the Application was filed. Applicants submit that the rejection of claims 52-57 is rendered moot in view of the amendments submitted herewith, which include cancellation of these claims.

As described in the specification and recited in the instant claims, the invention relates to an isolated ANT1 fusion protein comprising an ANT1 polypeptide fused to at least one additional polypeptide sequence, wherein the ANT1 polypeptide has at least 95% amino acid sequence identity to the sequence of a human ANT1 polypeptide set forth in SEQ ID NO:31 and is capable of binding an ANT ligand. In a particular embodiment, the invention is directed, in pertinent part, to an isolated ANT1 fusion protein comprising an ANT1 polypeptide fused to at least one additional polypeptide sequence cleavable by a protease, wherein the ANT1 polypeptide is separable from the fusion protein by cleavage with the protease, and wherein the ANT1 polypeptide has at least 95% amino acid sequence identity to the sequence of a human ANT1 polypeptide set forth in SEQ ID NO:31 and is capable of binding an ANT ligand.

Applicants submit that the specification reasonably conveys to a skilled artisan that Applicants were in possession of the claimed invention at the time of filing by providing sufficiently detailed and relevant identifying characteristics of the claimed ANT1 fusion proteins. The instant Application describes that a fusion protein may comprise the amino acid sequence of human ANT1 (SEQ ID NO:31) or an amino acid sequence at least 95% identical to the human ANT1 polypeptide sequence set forth in SEQ ID NO:31, thus providing a detailed, structural chemical formula from which a skilled person may make and use the claimed fusion protein (*see* page 18, lines 1-27 and references cited therein). The specification also describes polypeptide sequences that may be fused to the ANT1 polypeptide, for example, polypeptides such as a histidine tag or GST that are useful for facilitating purification and detection of the ANT1 polypeptide (*see, e.g.,* page 25, line 12 through page 27, line 10). Furthermore, an illustration of how to make and use ANT fusion proteins is provided in the Application in detailed working examples (*see* Examples 1-3).

Applicants therefore respectfully submit that as recited in the instant claims and supported by the present specification, the Application reasonably conveys to a person skilled in the art that Applicants possessed the claimed invention at the time of filing. Applicants submit that the present Application satisfies all requirements under 35 U.S.C. § 112, first paragraph, and respectfully request that rejection of the claims be withdrawn.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The PTO rejects claims 47-51 and 56-57 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Specifically, the PTO asserts that claims 47, 51, and 56 are unclear regarding whether the subject matter encompasses only "human" ANT sequences, as recited in claims 47 and 51, or "animal" ANT sequences, as recited in claim 56. The PTO also asserts that the claims are unclear with respect to whether the claims are broad and encompass any ANT1 sequence (claim 56) or any ANT1 sequence 95% identical to SEQ ID NO:31 (claims 47 and 51).

Applicants respectfully traverse this rejection and submit that the present claims particularly point out and distinctly claim the subject matter that Applicants regard as their invention. Applicants have cancelled claim 56 without acquiescence to any rejection and without prejudice to prosecuting this subject matter in a related divisional, continuation, or continuation-in-part application.

Applicants submit that in view of the amendments submitted herewith, the claims clearly point out that the claimed subject matter encompasses an isolated ANT1 fusion protein comprising an ANT1 polypeptide fused to at least one additional polypeptide sequence, wherein the ANT1 polypeptide has at least 95% amino acid sequence identity to the sequence of a human ANT1 polypeptide as set forth in SEQ ID NO:31. In certain embodiments, the claims particularly point out that the ANT1 polypeptide moiety of the fusion protein is separable from the additional polypeptide sequence by cleavage with a protease. Accordingly, Applicants submit that the present claims unambiguously and clearly recite the subject matter encompassed by Applicants' invention.

Applicants therefore respectfully submit that the application is in full compliance with the requirements of 35 U.S.C. § 112, second paragraph, and request that these rejections be withdrawn.

Applicants respectfully submit that all claims in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. In the event that the Examiner believes a teleconference will facilitate prosecution of this case, the Examiner is invited to telephone the undersigned representative at 206-622-4900.

Respectfully submitted,
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